inventions. Claims 10, 14 and 16-18 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1-5 and 24-28 are rejected under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb (U.S. Patent 5,869,242). Claims 1-7 and 24-30 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Sutherland et al. (U.S. Patent 5,985,619). Claims 1-5, 10, 14 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster (U.S. Patent 6,074,823). Claims 1-5, 8-9, 11-13, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli (U.S. Patent 5,808,300). Claims 1-5, 10, 14, 16 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in the view of Sutherland et al. Claims 1-5, 8-9, 11-13, 15, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli and further in view of Sutherland et al. Claims 1-5, 10, 14, 16-18 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in view of Caprioli.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In the Office Action, the Examiner has made the Restriction Requirement final. Therefore, claims 19-23 are withdrawn from consideration as drawn to non-elected inventions.

It is respectfully submitted that claims 19-23 have been canceled without prejudice by the instant amendment. Applicants reserve the right to pursue the subject matter of these canceled claims in a divisional application.

Claim 10 and dependent claims 14 and 16-18 are rejected under 35 U.S.C. §112, second paragraph. The Examiner contends that the phrase "capable of" recited in claim 10 renders the claim indefinite.

It is respectfully submitted that claim 10 has been amended to substitute the recitation "which controls" for the term "capable of". Claim 10, as amended, is not indefinite. Accordingly, the rejection of claims 10, 14 and 16-18 under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is therefore respectfully submitted.

Claims 1-5 and 24-28 are rejected under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb (U.S. Patent 5,869,242).

It is observed that independent claim 1 is directed to a method of detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule by subjecting the test nucleic acid molecule to *base-specific* cleavage to generate oligonucleotide fragments, separating the fragments based on mass by MALDI-TOF MS and/or other equivalent procedure to produce a fingerprint of the fragments comprising one or more peaks wherein a peak represents the mass of each fragment, and identifying an altered peak relative to a reference nucleic acid molecule subjected to the same procedure, wherein the presence of an altered peak is indicative of a difference of one or more nucleotides in said test nucleic acid molecule. Claim 2, which depends on claim 1, recites that the test nucleic acid molecule is amplified prior to base-specific cleavage. Claims 3-5, which ultimately depend upon claim 1, further characterize the length of the oligonucleotide fragments. Independent claim 24 is directed to a method for identifying and/or locating a mutation in one or more bases in a target nucleic acid molecule. Claim 24 recites the same method steps as those of claim 1. Claim 25 depends on claim 24 and recites that the test nucleic acid molecule is amplified prior to base-specific cleavage. Claims 26-28 ultimately depend upon claim 24 and further characterize the length of the oligonucleotide fragments.

The Examiner contends that Kamb teaches a method of detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule. According to the Examiner, Kamb teaches subjecting a test nucleic acid molecule to base-specific cleavage to generate oligonucleotide fragments (claims 1-3 and 5, and column 6, line 50 to column 8, line 37); separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment (Tables II and III, and Example IV, column 6, line 50 to column 8, line 37); and identifying an altered peak relative to a reference nucleic acid molecule subjected to the same procedure, wherein the presence of an altered peak is indicative of a difference of one or more nucleotides in the tested nucleic acid molecule (claims 1 and 3, and Table II). The Examiner also contends that Kamb teaches that the nucleic acid molecule to be tested can be amplified by PCR prior to base-specific cleavage (column 4, lines 36-46 and column 7, lines 39-54). Additionally, the Examiner contends that Kamb teaches that the base-specific cleavage results in oligonucleotide fragments of from about 2 bases to about 1000 bases (Table III). Accordingly, the Examiner concludes that Kamb teaches the claimed invention as defined in claims 1-5 and 24-28.

Applicants respectfully submit that the Kamb patent at column 6, line 50 to column 8, line 37, which is relied upon by the Examiner as allegedly providing the cleavage of a test nucleic acid molecule, only shows the cleavage of a test nucleic acid molecule by a restriction enzyme. Unlike *base-specific* cleavage (e.g., cleavage at uracil by uracil-N-glycosylase) as taught by the present specification, cleavage by restriction enzymes is only *sequence-specific*.

It is respectfully submitted that base-specific cleavage is nowhere taught by Kamb. Moreover base-specific cleavage results in a more efficacious and accurate detection of

nucleotide differences as compared to a detection achieved by a method involving sequence-specific cleavage. In particular, multiple restriction enzymes would be required in order to fully characterize the changes in bases in a particular fragment, as there is likely to be regions of DNA which are devoid of sites for restriction enzymes. In contrast, with base-specific cleavage, in effect only four separate enzymes would be required in order to digest a single base at a time in order to determine the sequence of a particular location. A single base-specific enzyme is likely to be highly effective anywhere in the DNA to generate a small enough fragment in order to be analyzed by MALDI-TOF.

Applicants observe that Kamb briefly mentions that nucleotide analogs can be incorporated into the nucleic acid molecule (to be tested) during the process of amplification and the amplified DNA can be subsequently cleaved. Specifically, Kamb states at column 4, lines 36-45:

> "One useful substitution is to incorporate deoxyuridine into amplified DNA. This is useful for producing small fragments by later digesting the amplified DNA with uracil-N-glycosidase."

However, Kamb does not anywhere describe how a nucleic acid molecule is amplified in the presence of nucleotide analogs such as uracil, how the amplified product is cleaved by uracil-N-glycosidase, or how or whether the oligonucleotide fragments as a result of the cleavage, if any, are separated by MALDI-TOF MS to produce a fingerprint. Kamb does not provide any disclosure as to whether a difference of one or more nucleotides between a test nucleic acid molecule and a reference nucleic acid molecule can be detected by amplifying the test molecule in the presence of uracil, subsequently subjecting the amplified product to cleavage with uracil-N-glycosidase and separating the resulting fragments by MALDI-TOF MS.

In this regard, Applicants respectfully submit that the prior art must provide an enabling disclosure of how to make and use the claimed subject matter for anticipation purposes. Scripps Clinic & Research Foundation v. Genetech, Inc., 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). Applicant respectfully submits that neither those specific passages of the Kamb patent referenced by the Examiner, nor the entire disclosure of the Kamb patent, provides an enabling teaching for a method of detection of a difference of one or more nucleotides between a test nucleic acid molecule and a reference molecule using base-specific cleavage to produce a fingerprint, as presently claimed.

Accordingly, Applicants respectfully submit that the Kamb patent does not teach the present invention. Withdrawal of the rejection of claims 1-5 and 24-28 under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb is therefore respectfully requested.

Applicants further respectfully submit that although the Kamb reference may have provided a motivation for those skilled in the art to try to use uracil and uracil-N-glycosylase in a method of detection involving MALDI-TOF MS, "obvious to try" is not the standard under 35 U.S.C. §103. In re Fine, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1599 (Fed. Cir. 1988). In particular, there is no indication anywhere in the Kamb reference that those skilled in the art would reasonably expect that such an attempt would be successful. Accordingly, it is respectfully submitted that the instantly claimed methods are also unobvious in view of the Kamb reference.

Claims 1-7 and 24-30 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

The Examiner admits that Kamb does not teach the method wherein the base specific cleavage is uracil-specific and mediated by uracil-N-glycosylase. However, the Examiner points

out that Sutherland et al. teach a method wherein the base-specific cleavage is uracil-specific and mediated by uracil-N-glycosylase (column 9, lines 4-29). The Examiner contends that one skilled in the art, by employing scientific reasoning, would have utilized the uracil-specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. in the mass spectrometry to assess DNA sequence polymorphisms taught by Kamb in order to improve the sequencing of nucleic acids containing unconventional bases. The Examiner further contends that one skilled in the art would have been motivated to do so in order to achieve the express advantages noted by Sutherland et al., namely, uracil-N-glycosylase (UNG) is commercially available and is useful to specifically cleave uracil.

Applicants respectfully submit that it is improper for the Examiner to reject the instant claims on the ground that one skilled in the art would have combined the teaching of Kamb with that of Sutherland et al. by "employing scientific reasoning." "Scientific reasoning" is not the standard for determining the patentability of the present claims.

In addition, Applicants respectfully submit that Sutherland et al. merely teach the availability of uracil-N-glycosylase as a uracil-specific cleavage enzyme. Sutherland et al. do not provide any teaching or suggestion for those skilled in the art to use uracil and uracil-N-glycosylase in a method of detecting nucleotide differences.

The Examiner has identified certain "express advantages" of Sutherland et al. Applicants are presently unaware of the relevance of the alleged advantages. Assuming pro arguendo, the existence and relevance of such advantages, Applicants submit that these advantages alone provide no motivation for those skilled in the art to modify the Kamb method. In this regard, Applicants submit that the suggestion or teaching to combine the references must

be found in the prior art, not in applicants disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Accordingly, it is respectfully submitted that the rejection of claims 1-7 and 24-30 under 35 U.S.C. §103 (a) based on the combination of Kamb and Sutherland et al. is improper. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-5, 10, 14 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster (U.S. Patent 6,074,823).

The Examiner admits that Kamb does not teach the method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS. However, the Examiner contends that Koster teaches a method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS (column 5, lines 22-35).

As submitted above, Kamb does not teach or suggest a method of detection involving base-specific cleavage, as instantly claimed. This deficiency is not cured by the Koster reference. Thus, the claimed methods of detection involving base-specific cleavage and a computer capable of controlling a method of detecting mutation by MALDI-TOF MS, are not taught or suggested by the Kamb reference and the Koster reference, taken individually or in combination. Accordingly, the rejection of the claims under 35 U.S.C. §103 (a) over Kamb in view of Koster, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-5, 8-9, 11-13, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli (U.S. Patent 5,808,300).

The Examiner admits that Kamb does not teach the method of subjecting fragmentation products to further separation by the post-source-decay method. However, the

Examiner contends that Caprioli teaches the method of subjecting fragmentation products to further separation by a post-source-decay method (column 3, lines 9-11).

Applicants first submit that Caprioli teaches the application of a post-source-decay method in separating peptides, but not oligonucleotides involved in the claimed methods. There is no teaching or suggestion in Caprioli as to whether the method of the post-source-decay method disclosed by Caprioli can be successfully applied in separating oligonucleotide fragments resulting from base-specific cleavage. Furthermore, Applicants submit that neither Kamb nor Caprioli, nor the combination of the two, teach or suggest a method of detection involving base-specific cleavage, as instantly claimed. Accordingly, the claimed methods of detection involving base-specific cleavage and subjecting oligonucleotide fragments to further separation by a post-source-decay method, are not taught or suggested by the Kamb reference and the Caprioli reference, individually or in combination. Therefore, withdrawal of the rejection under 35 U.S.C. §103 (a) over Kamb in view of Caprioli, is respectfully requested.

Claims 1-5, 10, 14, 16 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in the view of Sutherland et al.

The Examiner admits that Kamb and Koster taken together do not teach a method wherein the cleavage is uracil-specific and mediated by uracil-N-glycosylase. According to the Examiner, those skilled in the art would have applied the uracil specific base cleavage mediated by uracil-N-glycosylase, as taught by Sutherland et al., in the computerized mass spectrometry to assess DNA sequence polymorphisms as taught by Kamb in view of Koster. The Examiner contends that those skilled in the art would have done so after "employing scientific reasoning" and because Sutherland et al. suggest the advantages of uracil-N-glycosylase.

Applicants respectfully reassert that Sutherland et al. merely teach the availability of uracil-N-glycosylase as a base-specific cleavage enzyme. Sutherland et al. do not teach or suggest utilizing the uracil base and uracil-N-glycosylase in a method of detecting nucleotide differences as taught by Kamb. The advantages allegedly provided by Sutherland et al., i.e., that uracil-N-glycosylase (UNG) is commercially available and is useful to specifically cleave uracil, are irrelevant and provide no motivation for those skilled in the art to modify the Kamb method. Accordingly, the Examiner's rejection of the instant claims based on the combination of Kamb, Koster and Sutherland et al. is improper. Therefore, withdrawal of the rejection under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in the view of Sutherland et al., is respectfully requested.

Claims 1-5, 8-9, 11-13, 15, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli and further in view of Sutherland et al.

The Examiner admits that Kamb and Caprioli taken together do not teach a method wherein the cleavage is uracil-specific and mediated by uracil-N-glycosylase. However, the Examiner contends that Sutherland provides such teaching and motivation for those skilled in the art to modify the method as taught by Kamb and Caprioli.

As submitted above, Sutherland et al. merely teach the availability of uracil-N-glycosylase as a base-specific cleavage enzyme. Sutherland et al. do not teach or suggest utilizing the uracil base and uracil-N-glycosylase in a method of detecting nucleotide differences as taught by Kamb. Neither do Sutherland et al. provide any motivation for those skilled in the art to modify the Kamb method. Accordingly, the Examiner's rejection of the instant claims based on the combination of Kamb, Caprioli and Sutherland et al. is improper. Therefore,

withdrawal of the rejection under 35 U.S.C. §103 (a) over Kamb in view of Caprioli and further in the view of Sutherland et al., is respectfully requested.

Claims 1-5, 10, 14, 16-18 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in view of Caprioli.

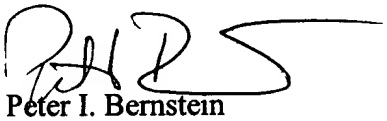
The Examiner admits that Kamb in view of Koster does not teach a method of subjecting the fragments to further separation by post-source-delay method. However, the Examiner contends that such teaching is provided by Caprioli. The Examiner further argues that those skilled in the art would have been motivated to combine and substitute a further separation by post-source-decay method of Caprioli into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Koster in order to achieve the express advantages, as noted by Caprioli, of a method which is used in order to obtain sequence verification.

Applicants respectfully submit that Caprioli does not teach or provide a suggestion as to whether post-source-decay method disclosed by Caprioli can be successfully applied in separating oligonucleotide fragments resulting from base-specific cleavage. Furthermore, Applicants submit that Kamb and Koster, taken together, do not teach or suggest a method which involves base-specific cleavage, as discussed above. Such deficiency is not cured by the Caprioli reference. Thus, the three cited references, Kamb, Koster and Caprioli, either taken individually or in combination, do not teach or suggest the instantly claimed methods which employ base-specific cleavage and post- source-decay for separating oligonucleotide fragments. Accordingly, the rejection of claims 1-5, 10, 14, 16-18 and 24-28 under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in view of Caprioli, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the instant amendment, captioned "**Version with Markings to Show Changes Made.**"

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Peter I. Bernstein
Registration No. 43,497

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
Telephone: 516-742-4343
PIB/XZ:ab

Enclosure: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please cancel claims 19-23 without prejudice.

Please amend the claims as follows:

10. (Amended) A computer program [capable of controlling] which controls a method of detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule, said method comprising subjecting the test nucleic acid molecule to base specific cleavage to generate oligonucleotide fragments, separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS [and/or]or other equivalent procedure to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment and identifying an altered peak relative to a reference nucleic acid molecule subjected to the same procedure, wherein the presence of an altered peak is indicative of a difference of one or more nucleotides in said tested nucleic acid molecule.

24. (Amended) A method for identifying [and/or]or locating a mutation in one or more bases in a target nucleic acid molecule, comprising subjecting the [test] target nucleic acid molecule to base specific cleavage to generate oligonucleotide fragments, separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS [and/or]or other equivalent procedure to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment, and identifying an altered peak

relative to a reference nucleic acid molecule subjected to the same procedure, wherein the presence of an altered peak is indicative of[a difference of one or more nucleotides in said test] a mutation in one or more bases in said target nucleic acid molecule.

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